Original Basic Research

Estimation of GFR in Patients With Cystic Fibrosis: A Cross-Sectional Study

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Abstract

Background: Patients with cystic fibrosis (CF) have frequent infectious complications requiring nephrotoxic medications, necessitating monitoring of renal function. Although adult studies have suggested that cystatin C (CysC)-based estimated glomerular filtration rate (eGFR) may be preferable due to reduced muscle mass of patients with CF, pediatric patients remain understudied.

Objective: Our objective was to determine which eGFR formula is best for estimating glomerular filtration rate (GFR) in pediatric patients with CF.

Methods: A total of 17 patients with CF treated with nephrotoxic antibiotics were recruited from the Children's Hospital at London Health Sciences Centre, London, Ontario, Canada. ^{99}Tc DTPA GFR (measured GFR [mGFR]) was measured with 4-point measurements starting at 120 minutes using a 2-compartmental model with Brøchner-Mortensen correction, with simultaneous measurement of creatinine, urea, and CysC. The eGFR was calculated using 16 known equations based on creatinine, urea, CysC, or combinations of these. Primary outcome measures were correlation with mGFR, and agreement within 10% for various eGFR equations.

Results: Mean mGFR was 136 ± 21 mL/min/1.73 m^2. Mean creatinine, CysC, and urea were 38 ± 10 μmol/L, 0.72 ± 0.08 mg/L, and 3.9 ± 1.4 mmol/L, respectively. The 2014 Grubb CysC eGFR had the best correlation coefficient ($r = 0.75$, $P = .0004$); however, only 35% were within 10%. The new Schwartz formula with creatinine and urea had the best agreement within 10%, but a relatively low correlation coefficient ($r = 0.63$, $P = .0065$, 64% within 10%).

Conclusions: Our study suggests that none of the eGFR formulae work well in this small cohort of pediatric patients with CF with preserved body composition, possibly due to inflammation causing false elevations of CysC. Based on the small numbers, we cannot conclude which eGFR formula is best.

Abrégé

Contexte: Les complications infectieuses nécessitant un traitement néphrotoxique sont fréquentes chez les patients atteints de fibrose kystique (FK), ce qui exige une surveillance de leur fonction rénale. Quoique des études chez l'adulte suggèrent qu'en raison de la réduction de la masse musculaire, la mesure du DFGe basée sur la cystatine C (Cys-C) serait la méthode à privilégier, les patients pédiatriques demeurent sous-étudiés.

Objectif: Déterminer la meilleure formule de calcul pour estimer le DFG chez les enfants atteints de FK.

Méthodologie: Au total, 17 patients atteints de FK et traités avec des antibiotiques néphrotoxiques ont été recrutés à l'hôpital pour enfants du London Health Sciences Centre de London (Ontario, Canada). Le DFG mesuré par ^{99}Tc DTPA (mDFG) a été mesuré en quatre points à partir de 120 minutes avec un modèle à deux compartiments, en appliquant la correction de Brøchner-Mortenson. Les taux de créatinine, d'urée et de CysC ont été mesurés simultanément. Le DFGe a été calculé à l'aide de 16 équations connues basées sur la créatinine, l'urée et la Cys-C, ou sur une combinaison de ces éléments. Les principales mesures de résultats étaient une corrélation avec le mDFG et une concordance à l'intérieur de 10 % avec les valeurs de plusieurs équations de DFGe.

Résultats: Le mDFG moyen s'établissait à 136 ± 2 ml/min/1,73 m^2. Les taux moyens de créatinine, de Cys-C et d'urée étaient respectivement de 38 ± 10 umol/L, $0,72 \pm 0,08$ mg/L et $3,9 \pm 1,4$ mmol/L. Le DFG obtenu par l'équation de Grubb 2014 avec la CysC présentait le meilleur coefficient de corrélation (r=0,75, p=0,0004), mais seulement 35 % des valeurs avaient une concordance à l'intérieur des 10 %. La nouvelle formule de Schwartz avec la créatinine et l'urée a obtenu le pourcentage le plus élevé de concordance à l'intérieur des 10 %, mais son coefficient de corrélation était relativement faible (r=0,63, p=0,0065, 64% des valeurs à l'intérieur des 10%).

Conclusion: Ces résultats suggèrent qu'aucune des formules de calcul du DFGe testées n'a bien fonctionné dans notre cohorte d'enfants atteints de FK avec une constitution physique préservée, possiblement en raison d'une inflammation provoquant une élévation du taux de Cys-C. Compte tenu de ces résultats, nous ne pouvons déterminer laquelle parmi ces formules de DFGe est la meilleure.

What was known before

Cystatin C is a marker of glomerular filtration rate that is independent of muscle mass. It has been shown for patients with diseases such as spina bifida and muscular dystrophy to be a superior marker for the estimation of glomerular filtration rate (eGFR). Patients with cystic fibrosis often have wasting disease and reduced muscle mass.

What this adds

In this analysis with carefully conducted gold standard measurements of glomerular filtration rate, creatinine or cystatin C or a combination thereof was not able to estimate GFR reliably in this patient cohort of mostly pediatric patients with cystatin C, likely due to a combination of inflammation and other factors. The study suggests that in some special patient populations such as patients with cystic fibrosis, glomerular filtration rate should be measured rather than estimated.

Background

Patients with cystic fibrosis (CF) have infectious complications that frequently require nephrotoxic medications, particularly aminoglycosides. After lung transplantation, there is a very high prevalence of chronic kidney disease (CKD) in these patients.[1,2] The prevalence of CKD after lung transplantation may be particularly high due to the additional nephrotoxicity of calcineurin inhibitors.[3] Therefore, it is of paramount importance to measure kidney function in these patients for appropriate dosing of aminoglycosides and other medications. In adults with CF, the use of serum creatinine–based estimation of glomerular filtration rate (eGFR) has been questioned.[3] Several studies suggest that cystatin C (CysC) may be a superior marker of kidney function in adult patients with CF, as these patients often have wasting disease and abnormal muscle mass.[4-6] In children, however, the use of CysC-based eGFR has not been well studied. In 1 small study of 11 teenage patients with CF, there was a low prevalence of elevated CysC.[7] Studies comparing CysC-based eGFR with gold standard GFR measurements in these patients are scant. Moreover, the body composition of pediatric patients with CF may not be as severely affected compared with the adult population, as demonstrated by recent work suggesting that pediatric patients with CF have relatively normal body mass index (BMI) *z* scores.[8] This difference in body composition between pediatric and adult patients with CF may affect the relative use of different biomarkers in estimating GFR. There is growing evidence that specific populations require disease-specific eGFR approaches;[9] however, the best approach for the estimation of GFR in pediatric patients with CF has not been determined. We are only aware of 1 study that evaluated 53 patients (adult and pediatric) where CysC, creatinine, and tobramycin clearance were compared against [99]TcDTPA clearance, which left us without a clear answer as all methods showed considerable variation on Bland and Altman analysis and also suggested that CysC would not be useful.[10] We therefore embarked on a cross-sectional study of pediatric and young adult patients with CF who received multiple courses of nephrotoxic medications, with the intent to compare a wide variety of existing pediatric eGFR formulae using urea, creatinine, and CysC as biomarkers of GFR. We hypothesized that the importance of CysC would be much less in pediatric patients with CF with well-preserved body composition, as compared to adult patients with CF with more advanced wasting disease.

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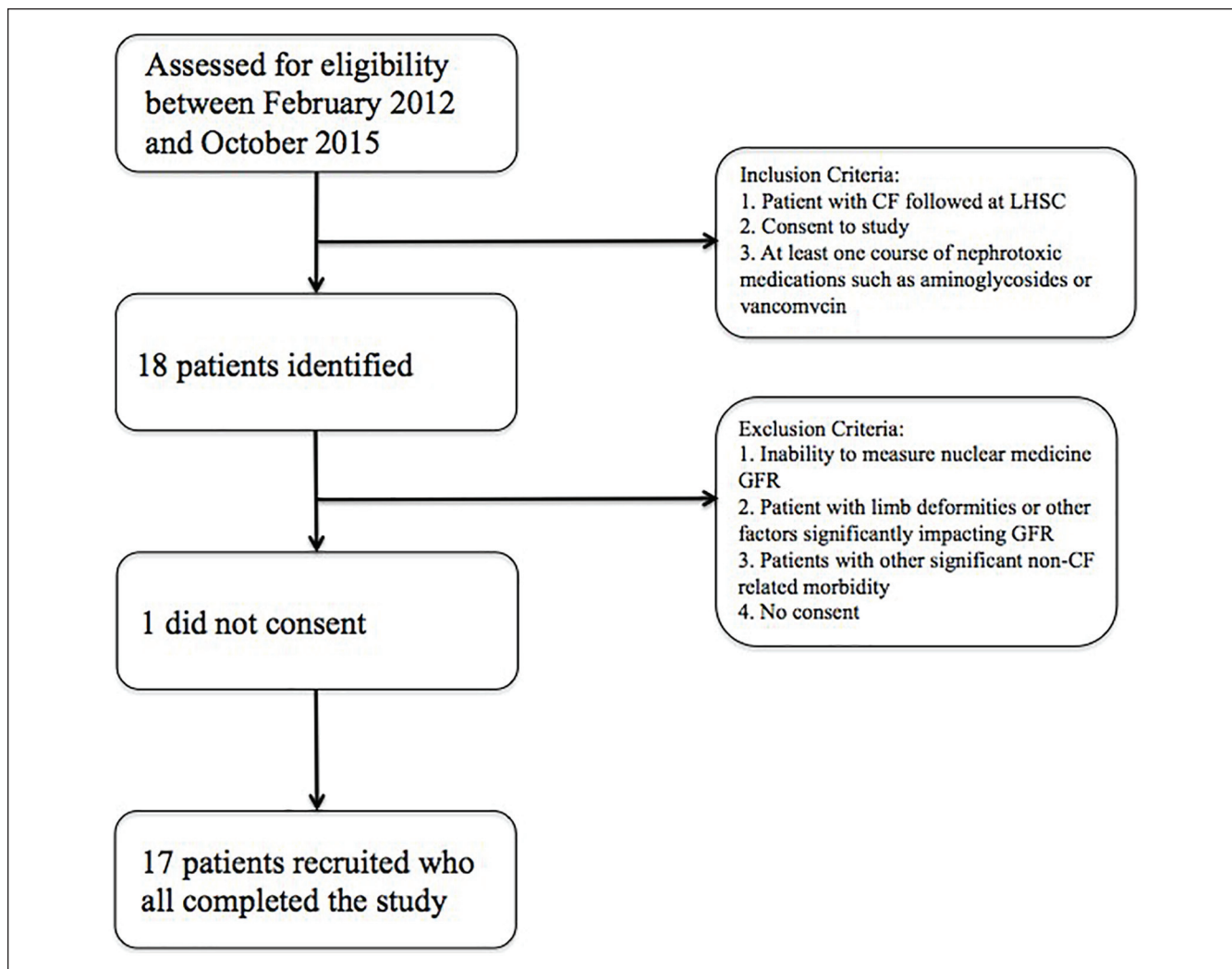
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Figure 1. Flow chart of patient recruitment and study participation.
Note. CF = cystic fibrosis; LHSC = London Health Sciences Centre; GFR = glomerular filtration rate.

Methods

Study Design

This cross-sectional cohort study adhered to the Declaration of Helsinki and was approved by The Research Ethics Board of the University of Western Ontario (REB 100967). Patients were recruited from February 2012 to October 2015. The primary purpose of the study was to determine which known eGFR formula would work best for pediatric patients with CF.

Setting

Patients were recruited from the University of Western Ontario's affiliated London Health Sciences Centre, a tertiary care hospital serving a catchment area of 2.6 million population in South Western and Northern Ontario, Canada, with a child and youth population of 629 000.

Participants

Patients with CF who received nephrotoxic medication such as aminoglycosides for serious infections were eligible for inclusion in this study. See Figure 1 for inclusion and exclusion criteria. Eighty-one patients were screened, and 21% were eligible. Consistent with the well-published data on the ethnic background of most patients with CF, our study population was predominantly white.

Methods

Patients underwent a [99]mTc DTPA GFR scan with a 4-point sampling approach 30 minutes apart starting at 120 minutes after injection according to Russell.[11] To accommodate the use of a 1-compartmental model with the possibility of slow phase of plasma clearance, we used the Brøchner-Mortensen correction.[12] To ensure the reliability of [99]mTc

Table 1. GFR Equations Used in the Study.

Equation name	Equation
Equations with serum CysC and without serum creatinine or urea	
Bökenkamp et al[17]	GFR (mL/min/1.73 m²) = 137/serum CysC − 20.4
Filler and Lepage[20]	GFR (mL/min/1.73 m²) = $10^{(1.962 + (1.123 \times \text{LOG (1/serum CysC)})}$
Grubb et al[21]	GFR (mL/min/1.73 m²) = 84.69 × serum CysC$^{-1.68}$ × 1.384 for age <14 y
Zappitelli et al[24] (Cys)	GFR (mL/min/1.73 m²) = 75.94 / [serum CysC$^{1.17}$] if renal transplant, × 1.2
Schwartz et al[23] improved 2012 (Cys only)	GFR (mL/min/1.73 m²) = (40.9 ± 0.3) × [1.8/CysC (mg/L)]$^{(0.931 \pm 0.020)}$
Grubb et al[22] standardized material 2014	GFR (mL/min/1.73 m²) = 130 × CysC$^{-1.069}$ × age[years]$^{0.117}$ − 7
Equations with serum creatinine and without serum CysC or urea	
Schwartz et al[23] improved 2012 (Cr only)	GFR (mL/min/1.73 m²) = (42.3 ± 0.3) × ((height (m) / Scr (mg/dL)))$^{(0.780 \pm 0.016)}$
Equations with serum urea and without serum CysC or creatinine	
Schwartz et al[23] improved 2012 (urea only)	GFR (mL/min/1.73 m²) = (41.0 ± 0.5) × [30/BUN (mg/dL)]$^{(0.613 \pm 0.024)}$
Equations with serum CysC and serum creatinine	
Bouvet et al[18]	[(SCr (μM) / 96)$^{-0.35\,(\pm 0.20)}$] × [(cysC (mg/L) / 1.2$^{-0.56\,(\pm 0.19)}$] × [(body weight (kg) / 45)$^{0.30\,(\pm 0.17)}$] × [age (years) / 14)$^{0.40\,(\pm 0.16)}$]
Schwartz et al[23] improved 2012 (Cys + Cr)	GFR (mL/min/1.73 m²) = (41.6 ± 0.3) × ((height (m) / Scr (mg/dL)))$^{(0.443 \pm 0.026)}$ × [1.8 / CysC (mg/L)]$^{(0.479 \pm 0.031)}$
Zappitelli et al[24] (Cys + Cr)	GFR (mL/min/1.73 m²) = (507.76 × $e^{0.003 \times \text{height}}$) / (CysC$^{0.635}$ × SCr$^{0.547}$ [μmol/L])
	If renal transplant, ×1.165
	If spina bifida, ×(SCr$^{0.925}$ [μmol/L]) / 40.45
Equations with serum creatinine and serum urea	
Schwartz et al[23] improved 2012 (Cr + urea)	GFR (mL/min/1.73 m²) = (41.9 ± 0.3) × ((height (m) / Scr (mg/dL)))$^{(0.662 \pm 0.021)}$ × [30 / BUN (mg/dL)]$^{(0.171 \pm 0.021)}$
Equations with serum CysC and serum urea	
Schwartz et al[23] improved 2012 (CysC + urea)	GFR (mL/min/1.73 m²) = (40.8 ± 0.3) × [1.8 / CysC (mg/L)]$^{(0.796 \pm 0.027)}$ × [30 / BUN (mg/dL)]$^{(0.157 \pm 0.022)}$
Equations with serum CysC, serum creatinine, and serum urea	
Schwartz et al[23] improved 2012 (Cr + CysC + urea)	GFR (mL/min/1.73 m²) = (41.5 ± 0.3) × ((height (m) / Scr (mg/dL)))$^{(0.417 \pm 0.026)}$ × [1.8 / CysC (mg/L)]$^{(0.431 \pm 0.032)}$ × [30 / BUN (mg/dL)]$^{(0.088 \pm 0.019)}$
Schwartz et al[23] improved 2012 (Final)	GFR (mL/min/1.73 m²) = (39.8 ± 0.4) × ((height (m) / Scr (mg/dL)))$^{(0.456 \pm 0.026)}$ × [1.8 / CysC (mg/L)]$^{(0.418 \pm 0.031)}$ × [30 / BUN (mg/dL)]$^{(0.079 \pm 0.018)}$ [(1.076 ± 0.013)$^{\text{male}}$] [height / 1.4]$^{(0.179 \pm 0.032)}$

Note. GFR = glomerular filtration rate; CysC = cystatin C; Cr =creatinine; SCr = serum creatinine; BUN = blood urea nitrogen.

DTPA measurements, standard radiochemical and radio-pharmaceutical purity tests were performed on each preparation of ^{99}mTc DTPA. The average purity, obtained from our radiopharmacy laboratory, was approximately 99%. The ^{99}mTc DTPA has been shown to have a good agreement with inulin and iothalamate clearance.[13]

Variables

The primary outcome was correlation between measured GFR (mGFR) and estimated GFR using CysC or creatinine or any combination of CysC, IDMS traceable creatinine, or urea. CysC was measured using a turbidimetric assay against international certified reference materials[14] on a Roche multiana-lyzer.[15] Serum creatinine was IDMS traceable since 2008.[16] Blood urea was measured using an enzymatic photometric

assay with a lower level of detection of 0.9 mmol/L. Microalbuminuria was measured using a turbidimetric assay with a lower detection limit of 3 mg/L on a Roche multiana-lyzer. The eGFR was calculated using the previously published Bökenkamp et al,[17] Bouvet et al,[18] CKiD,[19] Filler and Lepage,[20] Grubb et al,[21] new Grubb et al[22] with certified reference materials, the new Schwartz et al,[23] and Zappitelli et al[24] equations. The published equations are shown in Table 1.

Standard, not high-sensitivity, C-reactive protein (CRP) was measured using an immunoturbidimetric assay. All measurements were performed in the laboratories of London Health Sciences Centre.

Standard anthropometry was performed using high-precision scales and stadiometers in the outpatient clinic. Body surface area was calculated using the Mosteller[25] formula. The BMI *z* scores were calculated using the World Health

Organization (WHO) reference intervals.[26] Skin folds were measured using age-appropriate calipers. Skin fold *z* scores were calculated using Centers for Disease Control and Prevention (CDC) reference intervals.[27] Data were entered into an Excel spread sheet (Excel for Mac 2011, version 14.4.4.) and stored on a secure hospital drive.

Statistical Methods

Data analysis was performed using GraphPad Prism 5 for Mac OS X (GraphPad Inc, San Diego, California, version 5.0f). Data were analyzed for normal distribution using the D'Agostino-Pearson omnibus normality test. Correlation coefficients were calculated using appropriate parametric or nonparametric tests, mostly using the Pearson correlation coefficient for each XY pair (mGFR and eGFR), whereas bootstrap was used to construct confidence intervals for Pearson correlation coefficient (Table 3). A *P* value < .05 was considered significant. Comparison between groups was performed using analysis of variance (ANOVA). Given the low correlation coefficients, we did not include the analysis of bias and agreement using Bland and Altman[28] analysis other than for the bivariate Schwartz formula which had the highest within 10% rate.

Results

Participants

Six of the 17 patients were female. Mean age was 11.5 ± 8.3 years. Our patients had relatively well-preserved body composition with an average BMI *z* score of −0.01 ± 0.69. The average skinfold thickness was 7.3 ± 2.8 mm, producing a *z* score of −1.2 ± 1.2, which was significantly different from zero (*P* = .014, 1-sample *t* test). The patient characteristics are given in Table 2. The median number of nephrotoxic antibiotic treatment cycles was 2 (range = 1-7). Mean mGFR was 136 ± 21 mL/min/1.73 m² (range = 96-169 mL/min/1.73 m²). Of note, no patient had mGFR <90 mL/min/1.73 m². Mean creatinine was 38 ± 10 µmol/L, mean CysC was 0.72 ± 0.08 mg/L, and mean urea was 3.9 ± 1.4 mmol/L. Median CRP was 0.8 mg/L (range <0.6-22.9 mg/L). Not surprisingly, there was no correlation between CysC and skinfold *z* score, body surface area, BMI, height, or weight. The mean eGFRs based on all formulae used are provided in Table 2.

Regression Analysis

The *r* values and *P* values of the linear regression analyses for each of the 16 eGFR models are provided in Table 3. Statistically significant correlations between the gold standard GFR measurement and the eGFR using each of the formulae were observed with the new Grubb formula using certified reference intervals for CysC, the simple Schwartz

Table 2. Patient Characteristics.

Parameter	Mean	SD	Minimum	Maximum
Gender		6 F, 11 M		
Age, years	11.5	8.3	3.0	39.0
Height, cm	136.8	22.8	100.8	176.5
Weight, kg	34.7	15.1	16.4	57.7
Weight *z* score	0	1.02	−1.78	1.99
BMI, kg/m²	17.5	2.4	13.7	21
BMI *z* score	−0.01	0.69	−1.37	0.83
Skinfold, mm	7.3	2.8	3.8	13
Skinfold *z* score	−1.19	1.16	−2.89	0.53
Upper arm circumference, cm	21.1	3.7	16.3	25.5
FVC, L	3.2	1	0.8	4
FEV-1, L	1.7	0.8	0.8	3.1
FEV1/FVC	74.9	11.5	42	92
mGFR, mL/min/1.73 m²	136.0	21.4	95.7	168.7
Creatinine, µmol/L	38	10	24	52
CysC, mg/L	0.72	0.08	0.53	0.87
Urea, mmol/L	3.9	1.4	2.1	6.8

Note. F = female; M = male; BMI = body mass index; FVC = forced vital capacity; FEV-1 = forced expiratory volume; mGFR = measured glomerular filtration rate; CysC = cystatin C.

formula, the univariate new Schwartz formula for creatinine only, the bivariate new Schwartz formula for creatinine and CysC as well as for creatinine and urea, the multivariate Schwartz formula without sex and race and the final new Schwartz formula, as well as the bivariate Zappitelli formula (Table 3). The best correlation with the gold standard mGFR measurement was with the new Grubb formula using certified reference materials for CysC. The bivariate new Schwartz formula using urea and creatinine had the highest percentage of values within 10% of the gold standard mGFR (64%), but correlation coefficient of below 0.7. For this formula, bias was −12.37 ± 17.16% with a 95% limit of agreement from −46.01% to +21.26%. This was the only equation with greater than 60% of values within 10% of the mGFR. However, none of the formulae had an *r* value >0.75, indicating that significant variability was observed, irrespective of the biomarker used.

CRP (normal value <5.0 mg/L) was not normally distributed and ranged from <0.6 to 22.9 mg/L. Median CRP concentration was 0.8 mg/L (interquartile range = 0.6-3.1 mg/L), suggesting that there was a degree of inflammation in most patients. While there was a trend for higher CysC concentrations with higher CRP values, this did not reach statistical significance (Spearman *r* = 0.22, *P* = .11, 1-sided).

Discussion

In this single-center, cross-sectional study of children and young adults with CF, we found that our patients had relatively well-preserved body composition, with normal BMI *z*

Table 3. Regression Analysis of All 15 eGFR Models Used.

Parameter	(6) Grubb et al[22] Simple old Schwartz Cr	(7) Univariate Schwartz et al[23] Cr	(5) Univariate Schwartz et al[23] CysC	(8) Univariate Schwartz et al[23] BUN	(10) Bivariate Schwartz et al[23] Cr + CysC	(12) Bivariate Schwartz et al[23] Cr + BUN	(13) Bivariate Schwartz et al[23] CysC + BUN	(14) Multivariate Schwartz et al[23] all	(15) Multivariate Schwartz et al[23] final	(1) Bökenkamp et al[17]	(2) Filler and Lepage[20]	(3) Grubb et al[21]	(4) Zappitelli et al[24] CysC	(11) Zappitelli et al[24] CysC + Cr	(9) Bouvet et al[18]
Number of XY Pairs	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
Pearson r	0.7477	0.6596	0.1781	0.2449	0.5815	0.6315	0.2645	0.5965	0.6841	0.1764	0.1869	0.1963	0.1841	0.5048	0.1685
95% confidence interval	0.4313-0.9003	0.2619-0.8658	-0.3310-0.6069	-0.2673-0.6492	0.1399-0.8302	0.2165-0.8532	-0.2478-0.6611	0.1623-0.8372	0.3030-0.8766	-0.3326-0.6058	-0.3228-0.6126	-0.3141-0.6186	-0.3255-0.6108	0.03178-0.7931	-0.3571-0.6131
P value (2-tailed)	.0004	.0040	.4941	.3434	.0143	.0065	.3050	.0115	.0025	.4983	.4725	.4503	.4795	.0388	.5327
Significant	***	**	ns	ns	*	**	ns	*	**	ns	ns	ns	ns	*	ns
Within 10%	35.3%	11.8%	5.9%	23.5%	23.5%	64.7%	41.2%	41.2%	41.2%	29.4%	35.3%	0.0%	41.2%	58.8%	23.5%

Note. Cr = creatinine; CysC = cystatin C; BUN = blood urea nitrogen.
*p < 0.05, **p < 0.01, ***p < 0.001.

scores, only mildly decreased skinfold *z* scores, and no CKD. Most of the patients had an elevated CRP. The main objective was to assess the diagnostic performance of the existing eGFR formulae. Unfortunately, none of the published formulae showed a good agreement, suggesting that GFR should be measured in these patients. These findings are similar to those of Soulsby et al.[10]

The regression analysis of the various eGFR formulae with mGFR revealed significant but not strong correlation coefficients. The diagnostic performance of CysC-only-based eGFR methods was less than expected, except for the new Grubb formula using certified reference materials which had the best correlation coefficient of 0.7477 but relatively low accuracy within 10%.[22] The new bivariate Schwartz et al[23] formula using creatinine and urea had the best accuracy within 10%, but relatively low correlation coefficient.

The poor diagnostic performance of the CysC-based eGFR formulae was surprising. There are several likely reasons for this. First, none of our patients had impaired GFR. Studies have shown that eGFR formulae work best in the GFR range in which they were derived,[29] and all of the existing eGFR formulae were derived in populations with CKD. It has also been shown that the scatter of CysC against the mGFR is much tighter when the mGFR is abnormally low as compared with patients who hyperfilter or have normal GFR.[30] Of note, none of our patients had diabetes, which could lead to hyperfiltration. Second, our patients had relatively well-preserved body composition, particularly compared with the adult population with CF, which tends to have more advanced wasting disease.[31] Our study is in agreement with a recent study that demonstrated a well-preserved body composition in children with CF.[8] The significantly better diagnostic performance of CysC in adult patients is likely due to the low muscle mass of these patients.[4,32] Third, there was a high prevalence of elevated CRP in our patient cohort. It is well established that severe inflammation can lead to an increase in CysC, resulting in an underestimation of GFR.[33] Like all proteins, acute phase reactions may increase protein production. In our cohort, the correlation between CysC and CRP did not reach statistical significance, likely due to the small sample size. However, it is possible that the inflammation in our patient population contributed to the poor performance of CysC-based formulae. Taken together, there are multiple explanations for the rather disappointing diagnostic performance of CysC in this patient cohort.[15]

Overall, our results demonstrate that none of the eGFR formulae worked particularly well in this patient population. While the new bivariate Schwartz et al[23] formula had the best accuracy with 64.7% within 10%, the relatively low correlation coefficient was disappointing. The new Grubb formula using certified reference materials had the best correlation coefficient of 0.7477; however, only 35.3% were within 10%. There is growing evidence that combining different biomarkers improves the diagnostic performance for the estimation of GFR.[23,34,35] Based on the current study, however, none of the formulae work well. Given that most patients had a normal GFR, these results are not surprising.

Our study has several limitations. Due to the small number of participants, strategies to reduce bias could not be employed. Owing to the strict inclusion criteria, we have a small sample size. The lack of patients with impaired GFR also forms a limitation, as the results may not be generalizable to a population with impaired GFR. Although ^{99}Tc DTPA GFR measurements form a well-established gold standard method for the measurement of GFR, there is a small amount of plasma protein binding with DTPA, which may lead to overestimation of GFR.[36] However, this should have been addressed with the use of the Brøchner-Mortensen and Jodal[12] correction. Another limitation is the lack of reporting of bias and agreement as would be done with Bland-Altman plots, but given the poor correlation coefficients, we determined this analysis to be unnecessary. The well-preserved body composition in our patients limits the generalizability to patients with wasting disease. A strength of our study was the use of a high-precision 4-point mGFR method. Another strength of our study was the inclusion of a wide variety of available eGFR formulae. It should be noted that the availability of CysC is quite limited among the Canadian centers, and we are unaware of any other center that has a 1-hour turnaround time for CysC.[15]

Conclusions

In conclusion, our study does not support the use of eGFR formulae for the estimation of GFR in young patients with CF without wasting disease. The role of CysC remains uncertain and studies with larger sample size would be needed to definitely rule out that CysC will likely not be a good biomarker in patients with CF. While the correlation coefficient with the 2014 Grubb formula was best, it had a low percentage within 10%. The bivariate Schwartz formula from 2012 had the best percentage within 10%, but the correlation coefficient was much lower than that of the Grubb formula. We conclude that GFR should be measured in patients with CF with normal body composition. Given the limitations of this study, future prospective studies are needed to confirm these findings.

List of Abbreviations

ANOVA, analysis of variance; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CF, cystic fibrosis; CKD, chronic kidney disease; Cr, creatinine; CRP, C-reactive protein; CysC, cystatin C; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate.

Ethics Approval and Consent to Participate

This cross-sectional cohort study adhered to the Declaration of Helsinki and was approved by The Research Ethics Board of the University of Western Ontario (REB 100967). Parents, and if applicable, patients gave written informed consent. Where appropriate, written child assent was also obtained.

Consent for Publication

Availability of Data and Materials

Acknowledgments

Author Contributions

G.F. conceived of study (together with A.P.) and identified statistical methods, performed data merging and cleaning, statistical analysis, assisted with identifying relevant equations, provided formatting guidance and built the article framework, drafted and revised each section of the article with assistance, checked for compliance with STROBE statement, worked on multiple article revisions, and approved the final article. A.W. assisted with identifying STROBE criteria, performed the calculations of all estimated glomerular filtration rate (eGFR) formulae, worked on multiple article revisions, contributed to statistical sections, and approved the final article. A.P. contributed to the design of the study, assisted with identifying eligible patients with cystic fibrosis (CF), checked inclusion and exclusion criteria, recruited patients together with Jennifer Itterman and Tracy Gooyers, helped revise article, and approved the final article. E.F. assisted with identifying eligible patients with CF, recruited patients, pulled the patient data, helped revise article and contributed to statistical sections, and approved the final article. M.K. was instrumental with the ethics submission, helped G.F. and A.P. with the grant writing, helped draft introduction and discussion of the article, and approved the final article. All authors added intellectual content during article preparation and provided valuable feedback on various aspects of the article.

Declaration of Conflicting Interests

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References

1. Filler G, Sharma AP. High prevalence of chronic kidney disease in pediatric solid organ transplantation. *Pediatr Transplant*. 2009;13(1):7-10. doi:10.1111/j.1399-3046.2008.01077.x.

2. Benden C, Kansra S, Ridout DA, et al. Chronic kidney disease in children following lung and heart-lung transplantation. *Pediatr Transplant*. 2009;13(1):104-110. doi:10.1111/j.1399-3046.2008.01060.x.

3. Soulsby N, Greville H, Coulthard K, Doecke C. Renal dysfunction in cystic fibrosis: is there cause for concern. *Pediatr Pulmonol*. 2009;44(10):947-953. doi:10.1002/ppul.21086.

4. Beringer PM, Hidayat L, Heed A, et al. GFR estimates using cystatin C are superior to serum creatinine in adult patients with cystic fibrosis. *J Cyst Fibros*. 2009;8(1):19-25. doi:10.1016/j.jcf.2008.07.004.

5. Degen DA, Janardan J, Barraclough KA, et al. Predictive performance of different kidney function estimation equations in lung transplant patients. *Clin Biochem*. 2017;50(7-8):385-393. doi:10.1016/j.clinbiochem.2017.01.008.

6. Halacova M, Kotaska K, Kukacka J, et al. Serum cystatin C level for better assessment of glomerular filtration rate in cystic fibrosis patients treated by amikacin. *J Clin Pharm Ther*. 2008;33(4):409-417. doi:10.1111/j.1365-2710.2008.00932.x.

7. Sands D, Jaworska J, Urzykowska A, Ozimek M. Renal assessment in teenage patients with cystic fibrosis—preliminary report. *Dev Period Med*. 2015;19(1):98-104.

8. Murphy AJ, Hill RJ, Buntain H, White M, Brookes D, Davies PSW. Nutritional status of children with clinical conditions. *Clin Nutr*. 2017;36(3):788-792. doi:10.1016/j.clnu.2016.05.014.

9. Filler G, Lee M. Educational review: measurement of GFR in special populations. *Pediatr Nephrol*. 2017;33:2037-2046. doi:10.1007/s00467-017.

10. Soulsby N, Greville H, Coulthard K, Doecke C. What is the best method for measuring renal function in adults and children with cystic fibrosis. *J Cyst Fibros*. 2010;9(2):124-129. doi:10.1016/j.jcf.2009.12.002.

11. Russell CD. Optimum sample times for single-injection, multi-sample renal clearance methods. *J Nucl Med*. 1993;34(10):1761-1765.

12. Brøchner-Mortensen J, Jodal L. Reassessment of a classical single injection 51Cr-EDTA clearance method for determination of renal function in children and adults. Part II: empirically determined relationships between total and one-pool clearance. *Scand J Clin Lab Invest*. 2009;69(3):314-322. doi:10.1080/00365510802653680.

13. Barbour GL, Crumb CK, Boyd CM, Reeves RD, Rastogi SP, Patterson RM. Comparison of inulin, iothalamate, and 99mTc-DTPA for measurement of glomerular filtration rate. *J Nucl Med*. 1976;17(4):317-320.

14. Grubb A, Blirup-Jensen S, Lindstrom V, Schmidt C, Althaus H, Zegers I. First certified reference material for cystatin C in human serum ERM-DA471/IFCC. *Clin Chem Lab Med*. 2010;48(11):1619-1621. doi:10.1515/CCLM.2010.318.

15. Ismail OZ, Bhayana V, Kadour M, Lepage N, Gowrishankar M, Filler G. Improving the translation of novel biomarkers to clinical practice: the story of cystatin C implementation in Canada: a professional practice column. *Clin Biochem*. 2017;50(7-8):380-384. doi:10.1016/j.clinbiochem.2017.01.005.

16. Hetu PO, Gingras ME, Vinet B. Development and validation of a rapid liquid chromatography isotope dilution tandem mass spectrometry (LC-IDMS/MS) method for serum creatinine. *Clin Biochem*. 2010;43(13-14):1158-1162. doi:10.1016/j.clinbiochem.2010.05.018.

17. Bökenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J. Cystatin C—a new marker of glomerular filtration rate in children independent of age and height. *Pediatrics*. 1998;101(5):875-881. doi:10.1542/peds.101.5.875.

18. Bouvet Y, Bouissou F, Coulais Y, et al. GFR is better estimated by considering both serum cystatin C and creatinine levels. *Pediatr Nephrol*. 2006;21(9):1299-1306. doi:10.1007/s00467-006-0145-z.

19. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20(3):629-637. doi:10.1681/ASN.2008030287.

20. Filler G, Lepage N. Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? *Pediatr Nephrol*. 2003;18(10):981-985. doi:10.1007/s00467-003-1271-5.

21. Grubb A, Nyman U, Bjork J, et al. Simple cystatin C-based prediction equations for glomerular filtration rate compared with the modification of diet in renal disease prediction equation for adults and the Schwartz and the Counahan-Barratt prediction equations for children. *Clin Chem*. 2005;51(8):1420-1431. doi:10.1373/clinchem.2005.051557.

22. Grubb A, Horio M, Hansson LO, et al. Generation of a new cystatin C-based estimating equation for glomerular filtration rate by use of 7 assays standardized to the international calibrator. *Clin Chem*. 2014;60(7):974-986. doi:10.1373/clinchem.2013.220707.

23. Schwartz GJ, Schneider MF, Maier PS, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. *Kidney Int*. 2012;82(4):445-453. doi:10.1038/ki.2012.169.

24. Zappitelli M, Parvex P, Joseph L, et al. Derivation and validation of cystatin C-based prediction equations for GFR in children. *Am J Kidney Dis*. 2006;48(2):221-230. doi:10.1053/j.ajkd.2006.04.085.

25. Mosteller RD. Simplified calculation of body-surface area. *New Engl J Med*. 1987;317:1098. doi:10.1056/NEJM198710223171717.

26. de Onis M, Onyango A, Borghi E, Siyam A, Blossner M, Lutter C. Worldwide implementation of the WHO Child Growth Standards. *Public Health Nutr*. 2012;15(9):1603-1610. doi:10.1017/S136898001200105X.

27. Addo OY, Himes JH. Reference curves for triceps and subscapular skinfold thicknesses in U.S. children and adolescents. *Am J Clin Nutr*. 2010;91(3):635-642. doi:10.3945/ajcn.2009.28385.

28. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1(8476):307-310.

29. Sharma AP, Yasin A, Garg AX, Filler G. Diagnostic accuracy of cystatin C-based eGFR equations at different GFR levels in children. *Clin J Am Soc Nephrol*. 2011;6(7):1599-1608. doi:10.2215/CJN.10161110.

30. Huang SH, Sharma AP, Yasin A, Lindsay RM, Clark WF, Filler G. Hyperfiltration affects accuracy of creatinine eGFR measurement. *Clin J Am Soc Nephrol*. 2011;6(2):274-280. doi:10.2215/CJN.02760310.

31. Panagopoulou P, Fotoulaki M, Nikolaou A, Nousia-Arvanitakis S. Prevalence of malnutrition and obesity among cystic fibrosis patients. *Pediatr Int*. 2014;56(1):89-94. doi:10.1111/ped.12214.

32. Beringer PM, Owens H, Nguyen A, et al. Estimation of glomerular filtration rate by using serum cystatin C and serum creatinine concentrations in patients with human immunodeficiency virus. *Pharmacotherapy*. 2010;30(10):1004-1010. doi:10.1592/phco.30.10.1004.

33. Filler G, Witt I, Priem F, Ehrich JH, Jung K. Are cystatin C and β2-microglobulin better markers than serum creatinine for prediction of a normal glomerular filtration rate in pediatric subjects. *Clin Chem*. 1997;43(6, pt. 1):1077-1078.

34. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *New Engl J Med*. 2012;367:20-29. doi:10.1056/NEJMoa1114248.

35. Inker LA, Tighiouart H, Coresh J, et al. GFR estimation using β-trace protein and β2-microglobulin in CKD. *Am J Kidney Dis*. 2015;67:40-48.

36. Witzel SH, Huang SH, Braam B, Filler G. Estimation of GFR using β-trace protein in children. *Clin J Am Soc Nephrol*. 2015;10:401-409. doi:10.2215/CJN.04860514.